Case series

Motor neuroprosthesis implanted with neurointerventional surgery improves capacity for activities of daily living tasks in severe paralysis: first in-human experience

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ABSTRACT

Background Implantable brain–computer interfaces (BCIs), functioning as motor neuroprostheses, have the potential to restore voluntary motor impulses to control digital devices and improve functional independence in patients with severe paralysis due to brain, spinal cord, peripheral nerve or muscle dysfunction. However, reports to date have had limited clinical translation.

Methods Two participants with amyotrophic lateral sclerosis (ALS) underwent implant in a single-arm, open-label, prospective, early feasibility study. Using a minimally invasive neurointervention procedure, a novel endovascular Stentrode BCI was implanted in the superior sagittal sinus adjacent to primary motor cortex. The participants undertook machine-learning-assisted training to use wirelessly transmitted electrocorticography signal associated with attempted movements to control multiple mouse-click actions, including zoom and left-click. Used in combination with an eye-tracker for cursor navigation, participants achieved Windows 10 operating system control to conduct instrumental activities of daily living (IADL) tasks.

Results Unsupervised home use commenced from day 86 onwards for participant 1, and day 71 for participant 2. Participant 1 achieved a typing task average click selection accuracy of 92.63% (100.00%, 87.50%–100.00%) (trial mean (median, Q1–Q3)) at a rate of 13.81 (13.44, 10.96–16.09) correct characters per minute (CCPM) with predictive text disabled. Participant 2 achieved an average click selection accuracy of 93.18% (100.00%, 88.19%–100.00%) at 20.10 (17.73, 12.27–26.50) CCPM. Completion of IADL tasks including text messaging, online shopping and managing finances independently was demonstrated in both participants.

Conclusion We describe the first-in-human experience of a minimally invasive, fully implanted, wireless, ambulatory motor neuroprosthesis using an endovascular stent-electrode array to transmit electrocorticography signals from the motor cortex for multiple command control of digital devices in two participants with flaccid upper limb paralysis.

INTRODUCTION

Severe paralysis and impaired voluntary motor function can result from a variety of conditions affecting brain, spinal cord, peripheral nerve or muscle function, and contribute to a large global burden of disease. People with impaired voluntary motor function often lose the ability to perform instrumental activities of daily living (IADL) tasks, including communication, shopping and financial management, and have an increased need for nursing home care. IADL disability occurs in almost all patients with amyotrophic lateral sclerosis (ALS), with 75% of patients living at home requiring assistance with finances, remote communication and shopping, leading to dependence on a caregiver. However, in a significant proportion of patients, the motor cortex remains functionally intact.

Brain–computer interfaces (BCIs) hold promise to restore voluntary motor control of digitally enabled devices in paralyzed individuals. Scalp electroencephalogram (EEG)-based and near infrared spectroscopy BCIs have demonstrated the capacity to translate signals into device control commands and binary output (yes/no) communication in locked-in syndrome; however, complex daily system setup by caregivers or expert technicians has limited clinical translation. Implanted BCIs utilizing penetrating arrays or subdural arrays have demonstrated capacity for high-fidelity device control but require burr hole craniotomy for implantation. Penetrating array systems in particular have shown promise for high performance, including control of robotic limbs and personal computers. The high-performance...
power and data transmission requirements associated with penetrating arrays have created yet-to-be-overcome technical barriers for human implantation of a wireless and ambulatory system. The only report of an unsupervised, ambulatory implantable BCI utilized a subdural array and was limited to a single binary switch output for digital communication. We previously reported preclinical data demonstrating the potential for a permanently implanted endovascular Stentrode array to achieve comparable electrocorticography spectral content and bandwidth to epidural and subdural arrays.

We now describe the first in-human experience of a minimally invasive, fully implanted, wireless, ambulatory motor neuroprosthesis using an endovascular stent-electrode array to transmit electrocorticography signals from the motor cortex for digital device control in two participants with flaccid upper limb paralysis.

METHODS
Study design
The study design was a single-arm, open-label, prospective early feasibility trial with exploratory efficacy outcomes, conducted consistent with Food and Drug Administration (FDA) guidance of Early Feasibility Studies (EFS) of implantable BCIs. The protocol was approved by the St Vincent’s Hospital Melbourne Human Research Ethics Committee, Australia in November 2018 (Clinicaltrials.gov NCT03834857). The study objectives included exploratory efficacy outcomes, including signal fidelity, control of multiple motor impulse commands with training, and the use of the commands to control digitally enabled devices to conduct tasks that improve capacity for IADLs. Inclusion and exclusion criteria are listed in table 1 (online supplemental appendix 1). Dual antiplatelet therapy with aspirin and clopidogrel was commenced 14 days prior to the procedure and continued for at least 3 months. Single-agent aspirin therapy was continued for at least 12 months. Participant 1 underwent neurointervention implantation in mid-2019 and participant 2 in early 2020.

Device components
The endovascular motor neuroprosthesis contained a self-expanding monolithic thin-film stent-electrode array (Stentrode, Synchron, CA, USA) designed for intracranial delivery using catheter venography neurointervention. Sixteen sensors were positioned circumferentially on an 8 mm × 40 mm nitinol scaffold, connected to a 50 cm flexible transvascular lead and inserted into an inductively powered internal telemetry unit (ITU, Synchron, CA, USA) (online supplemental figure S1). Vascular electrocorticographic signal (0.125 μV/bit, 2 kHz sampling rate) was transmitted wirelessly to an external telemetry unit (ETU) using infrared light, which relayed the signal to a tablet (Windows Surface Book 2, Microsoft, WA, USA) via a mobile signal control unit (figure 1).

Neurointervention
Under general anesthesia and guided by 3D digital subtraction angiography, co-registered to presurgical magnetic resonance imaging (MRI) marked with motor cortex deployment targets,
Figure 2  Pre- and post-neurointervention imaging. Panel A displays the baseline computed tomography venography study of the superior sagittal sinus in sagittal, axial and coronal views for participant 1. Panel B panel displays the repeat study at 3 months, and Panel C at 12 months following implantation of the Stentrode in the superior sagittal sinus, which revealed no evidence of thrombosis, stenosis or device migration. Panel D shows the regions of lower limb blood-oxygen-level-dependent (BOLD) activation relative to cortical and vascular structures derived from a preoperative magnetic resonance imaging study, co-registered to the superior sagittal sinus on intra-operative 3D digital subtraction angiography image.

Figure 3  Training and testing timeline. The timeline depicts specific training and testing events that occurred following neurointervention. The number of runs performed for a given task is provided when tests were performed, presented in the order that the tasks were conducted.

Timeline
An interim period between neurointervention and training was required for wound recovery and optimization of radio communication between the telemetry units for data flow. The training period began when chest bruising was completely resolved, and a reliable infrared communication could be established. Training consisted of two planned sessions per week, conducted between days 50 and 92 post-neurointervention (across 13 sessions) for participant 1, and between day 42 and 53 post-neurointervention for participant 2 (online supplemental appendix 1). The neuroprosthesis was implanted immediately adjacent to the precentral gyrus (figure 2D). The lead was tunneled and connected to the ITU, which was inserted in a subcutaneous pocket in the chest on the left side in participant 1 and right side in participant 2. The participant was extubated in the angiography suite and subsequently discharged home (participant 1, day 4; participant 2, day 2).

A guide catheter was advanced into the superior sagittal sinus via the left jugular vein in participant 1 and right jugular vein in participant 2 (online supplemental appendix 1). The neuroprosthesis was implanted immediately adjacent to the precentral gyrus (figure 2D). The lead was tunneled and connected to the ITU, which was inserted in a subcutaneous pocket in the chest on the left side in participant 1 and right side in participant 2. The participant was extubated in the angiography suite and subsequently discharged home (participant 1, day 4; participant 2, day 2).
(across three sessions) for participant 2 (figure 3). Performance testing was conducted between days 93 and 238 post-neurointervention across six sessions for participant 1, and between days 53 and 106 post-neurointervention across five sessions for participant 2. Unsupervised home use began on days 86 and day 71 post-neurointervention for participant 1 and 2, respectively, without the need for subsequent expert decoder recalibration.

Training

Training was conducted in the home with a single neuroscientist (PY) either physically or remotely present using custom training software (Synchron). Participants engaged in initial motor mapping task sessions, where a battery of movements were attempted. The battery of movement-attempts included bilateral fist clenching, foot tapping and knee extension (quadriceps contraction). If the participants had residual muscle function associated with specific movement-attempts, they were instructed to only generate effort up to, but not more than, that required to generate an explicit contraction. Alternating periods of predefined attempted movements and rest (eg, ‘push down left ankle like on a brake pedal’ or ‘clench right fist’) were performed for 2–10s each, guided by on-screen cues. There were between 4 and 12 trials per run. Motor mapping sessions typically lasted 2 hours and were limited by what the participant could comfortably tolerate. Spectral features were optimized based on the motor mapping data and a custom machine-learning decoder was designed for each participant (online supplemental appendix 1). The decoder generated one of three potential commands every 100 ms: ‘no click’, ‘short click’ or ‘long click’. The participants used their eye-movements to control the cursor with an eye-tracker ( Tobii Dynavox, PA, USA) and made click selections using the motor neuroprostheses. Short clicks were used for typing (keyboard selections) and for single-click events. Long clicks were used for typing and to zoom/magnify the screen while searching or locking onto a target for fine-scale selections in the Windows 10 environment (online supplemental appendix video). The training period ended when an average click selection accuracy ≥90% was achieved across at least one run of a typing task (10 words; see Performance testing section for description of the click selection accuracy and typing task). At this point, the decoder design was fixed, and performance testing began. The participants were free to use the system unsupervised at home for control of Windows 10 with the available decoder at any given time. System setup was performed by the caregiver with no expert knowledge, which involved attaching the receiver (ETU) to the chest with medical adhesive and launching the decoding software on Windows 10.

Decoder

The custom decoder had a preprocessing, classification and click-logic layer. The preprocessing layer calculated normalized spectral power as features from the raw data. The classification layer predicted whether the features corresponded to rest or movement-attempts. The click-logic layer generated a short click when the classification layer predicted 3–9 consecutive movement-attempts (ie, 300–900 ms) immediately followed by a rest prediction. A long click command was initiated and maintained from the tenth consecutive movement-attempt prediction (ie, 1000 ms) until a subsequent rest prediction was made. This feature allowed the participants to toggle the screen magnification function for fine-scale selections.

For participant 1, the features were normalized power of 1 Hz bins between 4 and 30 Hz. A support vector machine (SVM) model was used for the classification layer, which classified neural signals into either movement-attempts or rest. The binary SVM was trained on the right quadriceps movement-attempt data because it yielded the highest offline classification accuracy. Accuracy was defined as the proportion of movement-attempts and rest that were classified correctly (online supplemental appendix 1). Decoder settings were fixed on the thirteenth training session (day 92 post-neurointervention) and required no further recalibration. For participant 2, the features were normalized average power of 5 Hz bins between 12 and 70 Hz during left ankle movement-attempts. A threshold classifier was used for the classification layer, which predicted movement-attempts if the feature crossed a given threshold level of normalized power. Low and high threshold levels were manually tuned, with the lower being easier to reach than the higher (ie, set closer to 0). The decoder defaulted to the high threshold level but automatically changed to the low level when the participant was typing by monitoring keystrokes. The decoder design was fixed on the third training session (day 53 post-neurointervention). The feature normalization constants were recalibrated at the beginning of each session, which took 30 s.

Performance testing

A typing task performed at various time points was used to assess system control performance (figure 3). The task involved the participant observing a displayed word for 2 s, typing the letters, then pressing the enter key using an on-screen keyboard. The list of possible words was derived from the 25 most frequently used nouns, verbs and adjectives as defined by the Oxford English Corpus (accessed from https://en.oxforddictionaries.com). The participant was presented with approximately 10 random words at a time. Several metrics were calculated per trial (ie, per word) and descriptive statistics were calculated across trials. Metrics included click selection accuracy, correct characters per minute and information transfer rate (online supplemental appendix 1).

The capacity of participants to perform IADL tasks were tested qualitatively. Key tasks were identified from a highly validated, generalizable IADL scale, including smart device (telephone) communication (texting, emailing, browsing) as well as shopping and financial management (online supplemental appendix 1). The tasks were arbitrarily designed for the participants’ needs, thereby utilising a pragmatic approach that identified the minimal level of functionality that would represent capacity for task independence.

RESULTS

Participant 1

A patient in their 70s living at home with their partner, presenting initially with left upper limb weakness in 2016, was subsequently diagnosed with cervical onset ALS (flail limb variant) on electromyographic testing in 2018. During screening, dementia was excluded by a neurologist (SL) and respiratory assessment revealed a forced vital capacity (FVC) of 3.25 (81%). At enrolment in mid-2019, assessment by the principal investigator (BC) revealed Medical Research Council (MRC) muscle power scores of 2/5 in the distal upper limbs (fingers, wrist, elbow) and 4/5 power in the proximal shoulder, declining further to 2/5 immediately pre-implant. Lower limb assessment revealed 4/5 power bilaterally. Functionally, the loss of ability to use a personal computer or smartphone for the purposes of remote communication, including messaging, emailing and browsing, made the participant dependent on the immediate presence of their caregiver to attend to their needs in relation to technology utilization. Bulbar assessment revealed hypophonia and was subjectively declining. A trial of eye-tracking as an assistive technology failed, attributable to the participant’s poor tolerance to

the lag-click function due to fatigue. Voice activation technology was also attempted without success due to soft voice.

**Participant 2**
A patient in their 60s, working part time, living at home with their partner and children presented initially with left biceps fasciculation in 2013, followed by diagnoses of cervical-onset ALS in 2015. Symptoms progressed with lower motor neurone weakness in upper limbs, mild dysarthria and wasting of the tongue. Screening revealed an FVC of 3.9 L (68%) and dementia was ruled out. Medication included riluzole 50 mg twice daily. Baseline neurologi- cal examination demonstrated 3/5 power in the fingers and wrist bilaterally and 4/5 in the elbow and shoulder bilaterally. Functional impairment involved inhibited use of the personal computer and digital devices for communication, adversely affecting work-related activity and independent activities at home. Lower limb assessment revealed 4/5 power bilaterally.

**Preliminary safety reporting**
All adverse event reporting was conducted according to Common Terminology Criteria for Adverse Events (CTCAE) V4.03 and reviewed by an independent medical monitor (RN). Data are reported for a period of 12 months post-neurointervention for participant 1 and 3 months post-neurointervention for participant 2. There were no serious adverse events for either participant. There were no device-related adverse events, including headache or infection. On day 1, participant 1 had a post-procedural-related adverse event involving an episode of syncope associated with two sinus pauses of 7.5 s and 6 s in duration, occurring while sitting in a chair. The participant was noted to be pale and unresponsive but still breathing while sitting. There was return of consciousness within 10 s while being repositioned supine. These isolated events were attributed to post-procedural vagal tone following consultation by the electrophysiology cardiologist and required no intervention.

**Neurointervention**
Contrast-enhanced 3D digital subtraction angiography performed immediately after device deployment demonstrated complete stent-electrode opening and device-wall apposition within the superior sagittal sinus, immediately adjacent to bilateral dorsome- dian precentral gyri. Contrast-enhanced head and neck CT venography studies, performed 3 and 12 months post-neurointervention for participant 1, and 3 months post-neurointervention for participant 2, were assessed by a neuroradiologist (PM) and revealed no evidence of device migration from baseline, venous thrombosis or stenosis for both participants (figure 2A–C).

**Training**
Participant 1 completed training on day 92 post-neurointervention by achieving an average click selection accuracy of 95.48% (100.00%, 89.29%–100.00%) (trial mean (median, Q1–Q3)) from 53 selections made across 10 words (during session 13). Participant 2 completed training on day 53 post-neurointervention by achieving an average click selection accuracy of 93.94% (100.00%, 87.50%–100.00%) from 60 selections made across 10 words (during session 3) (online supplemental appendix 1).

**Performance testing**
Table 1 summarizes the performance testing results. Metrics for each trial within each session are provided in the (online supplemental appendix 1). On average, participant 1 achieved a click selection accuracy of 92.63% (100.00%, 87.50%–100.00%) (trial mean (median, Q1–Q3)) across 748 selections made over 129 trials, at 13.81 (13.44, 10.96–16.09) correct characters per minute (CCPM) (figure 4). The participant achieved 1.31 (1.58, 0.92–1.58) bits/trial at an information transfer rate (ITR) of 0.32 (0.30, 0.24–0.41) bits s⁻¹ with the motor neuroprosthesis alone, and 4.39 (4.95, 3.80–4.95) bits/trial at an ITR of 1.08 (1.05, 0.86–1.30) bits s⁻¹ with the motor neuroprosthesis + eye-tracker. The participant successfully completed all qualitative everyday tasks (text: n=12, email: n=5, shopping: n=2, finance: n=2).

Participant 2 achieved an average click selection accuracy of 93.18% (100.00%, 88.19%–100.00%) across 569 selections made over 95 trials at 20.10 (17.73, 12.27–26.50) CCPM during the typing task. The participant achieved 1.33 (1.58, 0.94–1.58) bits/trial at an ITR of 0.46 (0.41, 0.28–0.63) bits s⁻¹ with the
motor neuroprosthesis alone, and 4.43 (4.95, 3.85–4.95) bits/trial at an ITR of 1.57 (1.40, 0.98–2.11) bits/s was transmitted with the motor neuroprosthesis + eye-tracker. The participant successfully completed all qualitative everyday tasks (text: n=5, email: n=1, shopping: n=1, finance: n=1).

DISCUSSION

We report preliminary early feasibility data demonstrating accurate multiple command control using a fully implanted endovascular motor neuroprosthesis delivered with minimally invasive neurointervention. Two participants with flaccid upper limb paralysis due to ALS and dependent on caregivers used the ambulatory motor neuroprosthesis in conjunction with eye-tracking to control Windows 10 and independently conduct remote communication, online shopping and banking tasks.

The rate of information transmission for the motor neuroprosthesis alone was comparable to that reported in the landmark study of a fully implanted BCI. Implantation of that system required burr hole craniotomy, 197 days of training prior to unsupervised home use and achieved a single binary click. The current study achieved unsupervised home use of multiple-click actions within 86 days (participant 1) and 71 days (participant 2) of neurointerventional surgery. Fast uptake of the system was achieved using eye-tracking for cursor navigation. We utilised eye-tracking in place of the previously reported raster scanning for cursor navigation as eye-movements were preserved in the participants. Multiple command control was achieved by extending the outputs of a binary classifier to three distinct commands based on temporal dynamics of cortical signal features. While scalp EEG systems can achieve single binary click selection, the current endovascular approach overcomes the problem of complex daily caregiver-dependent electrode setup. Furthermore, training data showing multiclass decoding with wide-band features (online supplemental appendix figure S5) suggest the potential for future improvements in information transfer rate by increasing the discrete units of motor impulse commands, or switches.

The superior sagittal sinus encompasses the lower limb region of primary motor cortex, which likely explains why the highest quality cortical signal was generated from lower limb movement-attempts. Future applications may make use of lower limb signal for ambulatory device control systems. Other devices requiring complex end-effector control may necessitate rapid alternating or concurrently performed movement-attempts to achieve adequate command function. Access to other regions of motor and sensory cortex are potentially provided by superficial veins, particularly the vein of Trolard which tends to run in the central sulcus encompassing the hand knob. Neutral activity recorded from deep folds in central sulci may be more information-rich than superficial regions and potentially accessible via cortical veins.

Loss of capacity to perform IADLs is a predictor of failure to live independently or the need for admission to a nursing home. The quantitative assessment of modern-day digitally enabled tasks that improve IADLs provides a challenge to the design of future clinical trials assessing efficacy of implantable BCIs. We selected tasks relating to a well-validated IADL scale and utilised a pragmatic approach by identifying the minimum performance required by the participants to qualitatively demonstrate independent task performance dependent on their clinical need. A limitation of this approach is that the results may not be generalizable to other patient populations. The population most likely to benefit from this technology include patients with upper limb paralysis, preserved motor cortex and preserved eye-movements. Paralysis occurs due to a highly heterogeneous mix of conditions, so design of future clinical trials will require a standardized approach to task performance assessment that is clinically meaningful across a range of conditions.

Other limitations include the low number of participants studied and requirement for larger numbers to make any conclusions on the short- and long-term safety profile. The neuroprosthesis was implanted inside a blood vessel in two participants, with no evidence of thrombosis on 12-month and 3-month CT venography, respectively. Preclinical data indicate that endothelialization of the device occurs within 45 days, reducing both thrombosis risk and improving electrocorticography signal quality. Pre-existing literature from transverse sinus stent placement using cerebral venography for idio-pathic intracranial hypertension suggests a rate of thrombosis or intracranial haemorrhage of less than 0.5%, comparing favourably to the reported risk profile of burr hole craniotomy for deep brain stimulation. However, further work is required to characterize the safety profile in a larger sample.

CONCLUSIONS

These first in-human data demonstrate the potential for an endovascular motor neuroprosthesis to achieve digital device control with multiple commands in people with paralysis and, when combined with eye-tracking, to improve functional independence. Further work is required to characterize the short- and long-term safety profiles as well as establish standardized task performance criteria for meaningful clinical outcomes to inform the design of a pivotal trial.

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PRECLINICAL DATA

Endothelialization
An animal study was performed to demonstrate rates of endothelialization using an identical test article to that implanted in the human participant. Experiments were performed in accordance with FDA Regulations of Good Laboratory Practices for Nonclinical Laboratory Studies CFR Title 21 Part 58 and applicable NIH and NCI Standard Operating Procedures. Sheep (Merino ewes), were implanted with a Stentrode within a clinically-relevant sized vessel (6 mm jugular vein). The Stentrode was delivered using the coaxial catheter system designed for human use, and animals were terminated at day 3 (n=2) and day 45 (n=4), perfused, stained with Haematoxylin and Eosin and embedded in plastic or paraffin (APS, MN). 3-day subjects presented with completely denuded endothelium and thin segmental fibrin deposition. Although endothelial tissue loss presented, there was no exhibited injury to the vascular walls, deemed typical of an acute time point by the contracted agency. 45-day subjects demonstrated maturation of neointimal tissue that was expected of an extended time point. Microscopic fibrin deposition was observed on the intima and struts of the recording head, with 95% of device covered by 45 days (Fig. S1).
PARTICIPANT

Ethics and regulatory approval
This was a first-in-human, single arm, open-label, prospective study approved by the Human Research Ethics Committee of St Vincent's Hospital, Victoria, Australia, in November 2018. Subsequent Research Governance Office approval was granted by The Royal Melbourne Hospital in January 2019. The Research Governance Office approval for the clinical recruiting site, Calvary Health Care Bethlehem, was granted in December 2018. Approval was granted under the Clinical Trial Notification (CTN) scheme of the Therapeutic Goods Administration (TGA) Australia (CTN Repository CT-2018-CTN-02369-1 v1.0) on 29th November 2018.

Recruitment
As per the inclusion criteria, participants with a motor score of >4/5 must report a subjective decline of upper limb extremity in the preceding four months resulting in functional impairment. The participants underwent screening to confirm eligibility and consented to the study. Inclusion criteria were satisfactorily met, including assessment of an fMRI demonstrating activation of primary motor cortex immediately adjacent to the superior sagittal sinus as well as an MR head and neck venography that demonstrated bilateral patent transverse sinuses and jugular veins by an interventional neuroradiologist (PM) and vascular neurologist (BC). Participants were assessed by a neurologist specialising in frontotemporal dementia (SL) to exclude dementia and assess capacity for informed consent. A respiratory assessment including pulmonary function tests and sleep study was performed. If follow up appointments satisfied anesthesia screening criteria the participants would progress to a final confirmation of suitability for general anesthetic and suitability for the procedure 2 weeks before implant. All other inclusion criteria were confirmed on day -1, with no exclusion criteria being met and the participant underwent the implantation via angiography. The participants were commenced on aspirin 300 mg daily and 75 mg of clopidogrel 14 days prior to the procedure. For participant 1, a point-of-care antiplatelet resistance test was performed seven days prior (VerifyNow, Accumetrics, CA), which revealed 11% resistance to clopidogrel. The decision was made by the treating interventional neuroradiologist (PM) to increase the dose to 150 mg daily. Repeat testing immediately prior to the procedure revealed adequate platelet inhibition of 30%.

Patient reported outcomes
Participant 1
At baseline, quality of life score (EQ-5D-5L) of 73 out of 100, reduced to 72/100 at day-7 post implant, and 70/100 at day-14 post-implant. This was maintained to month-4 follow-up and reduced at month-5 and month-6 follow-up at 65, further
reducing to 50/100 at month-12 follow-up. Hospital Anxiety and Depression Scale (HADS) score at baseline was D=3 and A=5. Over the duration of the trial a normal HADS score was maintained, although elevated compared to baseline (A=6/D=7) at month-12. Visual Analogue Scale (VAS) score, at baseline 0 out of 10, elevated post procedure to 1/10 from day-7 to day-21 post implant, returning to baseline from day-28 to month-5. VAS score increased at month-6 to 2/10 and 3/10 at month-12, with the patient reporting muscle pain secondary to progression of motor neuron disease.

Participant 2
The baseline quality of life score (EQ-5D-5L) was 45/100, increasing to 70/100 post-implant at day-14 follow up, reducing at day-28 to 65/100, increasing for month-2 and month-3 to 70/100 and reducing to 65 at month-4 follow up visit. Visual analogue numeric pain distress scale (VAS) at baseline scored 0/10. During follow-up the VAS was elevated at day-28 to 2/10 and returned to baseline for month-2 and month-4. HADS score measured at baseline of D=2 and A=5 and maintained normal levels throughout to month-4 follow up (A=3 D=2).

IMAGING-GUIDED DEVICE DELIVERY
Pre-operative MRI acquisition (MRI venography and functional MRI)
A pre-operative MRI investigation of the cortical and vascular structures, and cortical motor function was performed inside a Siemens MAGNETOM Prisma 3T scanner. The participant’s vital signs were monitored, and communication was achieved through a two-way intercom while he was inside the scanner. The structural volumes were acquired using a contrast-enhanced (C+MPRAGE) and non-contrast enhanced magnetization prepared rapid gradient echo (MPRAGE) sequence, and contrast-enhanced Time-resolved angiography With Interleaved Stochastic Trajectories (TWIST) sequence. The acquired volumes were utilized to inform decisions regarding participation eligibility and implantation planning. Two sets of functional volumes were acquired using a gradient-echo echo-planar imaging (GE-EPI) sequence while the participant performed a lower-limb motor task. The participant was presented with instructions on the screen to either “rest” or “attempt”. The task in the first and second set was to tap their right foot (repeated ankle plantar flexion and relaxation) and left foot, respectively, at a rate of ~1 Hz. Both rest and attempt blocks lasted for 15 s each. There were eight attempt and nine rest blocks as each experiment began and finished with a rest trial. The participant practiced the task outside of the scanner and were given verbal instructions prior to the scan via the intercom.

Co-registration of deployment target markers for implantation
Regions of significant Blood-Oxygenation-Level-Dependent (BOLD) signal fluctuation during the left and right lower limb movements were identified by fitting
a General Linear Model (GLM) to each dataset. Z-score maps were generated by contrasting the attempt and rest blocks for each functional set. The resulting BOLD activation maps for left and right foot tapping were co-registered to the C+MPRAGE space. The dorsomedial Primary Motor Cortex (M1) was identified in the C+MPRAGE volume based on the structural information and guided by the functional information by a neuroradiologist (PM). Three guide markers for device deployment were identified in the C+MPRAGE space. The portion of the superior sagittal sinus (SSS) immediately superior to the posterior margin of the dorsomedial M1 was marked (i.e., M1 marker). The anterior and posterior markers were placed 18 mm anterior and 22 mm posterior to the M1 marker, respectively (A and P marker; the total length of the recording head is 40mm). These markers encompassed portion of the Supplementary Motor Cortex (SMA), the M1 and the Primary Somatosensory cortex (S1), denoting the ideal deployment region of the stent electrode array for recording motor-related signals[1,2]. The C+MPRAGE volume with the three device deployment targets was co-registered to the pre-contrast 3D-Digital Subtraction Angiography (3D-DSA) volume acquired intraoperatively. Siemens’ automatic co-registration algorithm was used, and the result was visually inspected by the interventionalist.

**Endovascular device deployment**
The participant was admitted to the Royal Melbourne Hospital the evening prior to the procedure and CT head and neck with contrast was performed as a baseline non-invasive venography study. The participant was placed under general anaesthesia and the angiography procedure was commenced. The co-registration of fMRI of data points on a structural MRI were used to generate an anatomical target using the roadmap function utilising the contrast-enhanced rotational 3D-DSA. A working view on the lateral plane on one image intensifier was set and utilised to overlay the roadmap with the anatomical targets (A, P and M1). The internal jugular vein was visualised under ultrasound guidance and punctured immediately above the clavicle, in between the two heads of the sternocleidomastoid muscle. A 6-French sheath (Pinnacle, Terumo) was exchanged over a microwire into the jugular vein. 5000 units of intravenous heparin were administered. Under DSA visualisation a coaxial catheter system (Fathom 16 microwire, Boston Scientific, MN; 3Max, 6-French Benchmark, Penumbra, CA) was advanced to the target location in the superior sagittal sinus. Venous tortuosity due to arachnoid granulations had been anticipated following their visualisation on the baseline CT venography. This resulted in minor resistance to the advancing 6-French catheter. Once the catheter was in position, the stent electrode array (Stentrode, Synchron, CA) was preloaded into a custom designed 4-French delivery sheath with radio-opaque tip (Synchron, CA), flushed with normal saline and advanced inside the guiding catheter. The delivery sheath was advanced to a position 10 mm beyond anatomical target A. The 6-French guide catheter was
retracted to the proximal superior sagittal sinus, leaving the delivery sheath in position. The delivery sheath was then retracted and positioned to match anatomical target A with the distal marker. The stent electrode array was then unsheathed, utilising the high radio-opacity of the cable to ensure correct positioning during deployment in the superior sagittal sinus with symmetric wall apposition (Fig. 2; Video S1). Repeat angiography demonstrated unimpaired blood flow through the Stentrode, with visualisation of an arachnoid granulation penetrating through a cell in the stent-head, resulting in anchoring of the device in position. The coaxial catheter system was removed, and gentle manual compression was held over the jugular vein to achieve haemostasis around the transvascular lead. The extension lead was unscrewed from the proximal portion, and the transmission lead exiting the vessel was tunnelled subcutaneously into a chest pocket. The proximal end was connected to the ITU (Synchron, CA) and the unit was implanted into the subcutaneous chest pocket immediately inferior to the left clavicle. Under sterile conditions in the angiography suite, the ETU was transiently placed above the ITU and the system check confirmed data was flowing. The participant was extubated in the angiography suite, monitored in the Intensive Care Unit and discharged home two days later.

DECORER
Parameter optimisation
Participant 1
Motor mapping task runs with a variety of movements were performed over the 12 sessions between day 50 and day 86 post-surgery. The data was used to determine the ideal strategy for BCI control and optimise the parameters of the preprocessing and classification layer based on decoding accuracy. Offline binary classification accuracy of left foot, right foot and right quadriceps movement attempt was assessed through random permutation. Across 50 iterations, a binary SVM was trained using a unique combination of training and validation dataset and its accuracy was tested on a fixed test set for each movement type separately (the test sets were initially randomly sampled and remained fixed through the iterations, and there were at least 810 samples to classify). The results revealed that the right quadriceps movement attempts yielded the highest accuracy averaged across the permutations (78.7±1.2%; mean±SD), compared to right (66.5±5.7%, Wilcoxon rank-sum test \( p=6.9006\times10^{-18} \)) and left foot tapping attempts (55.5±2.3%, \( p=6.6045\times10^{-18} \); Fig. S5). Thus, we focused on the right quadricep movement attempts for future sessions. Between sessions 12 and 13, several typing tasks were performed using this decoder to optimise the parameters of the click-logic layer in the decoder. The decoder parameters were fixed from session 13 (day 92 post-surgery). All hyperparameters, except for C and \( \gamma \) of the SVC were manually optimised.
Participant 2
Based on acquired knowledge from participant 1, it was deemed that direct visual feedback of features may help with training. However, high dimensional features that worked well for the SVM could not be visualised. Considering these factors, along with the success of extending binary classification events into two discrete outputs based on duration of control (i.e., click-logic layer), we employed a threshold decoder that took a 1D average spectral feature as an input that could be directly visualised. The ideal control strategy, feature channels and frequency bands described above were chosen based on the highest correlation values between the motor mapping tasks and spectral power of specific bipolar pair channels calculated from specific movement attempt types in session 1. The participant practiced controlling the 1D average spectral feature across the threshold levels with direct visual feedback, and the normalization constants and threshold values were fine-tuned session to session. The participant could also manually calibrate the normalization constants himself by clicking on the F11 key when using the system, which took 30 s.

General design
Raw data was sampled at 2 kHz per channel and was passed through the decoder comprised of three layers, preprocessing layer, classification layer, and click-logic layer (Fig. S2). The preprocessing layer removed large artifacts and disconnection events using thresholds in temporal and spectral domain and extracts spectral power as features. The classification layer predicted whether the features represented the state of rest or movement-attempts. The click-logic layer translated sequences of prediction events from the classifier into three outputs, no click, short click and long click. Hyperparameters of the decoders were manually tuned through trial and error and exploring the motor mapping task data. Participant specific settings for the decoder used for testing are provided below.

Preprocessing layer
For participant 1, the spectral features were extracted from a 100 ms window at 100 ms strides (i.e., every 100 ms). To capture neural correlates of right quadriceps movement attempts, the data from channels 4, 10 and 13 were re-referenced to channel 16 then passed through a 50 Hz notch-filter for line-noise removal and a 4-30 Hz second second-order Butterworth bandpass filter. Then, the decibel normalized spectral power of 1 Hz bins between 4-30 Hz were calculated using the Thompson multi-taper method. Finally, the data bins were passed through a 1 s boxcar filter (across time), resulting in 78 features (3 channels x 26 frequency bins) per current data bin.
For participant 2, the spectral features were calculated from a 1000 ms window at 100 ms strides. To capture neural correlates of left foot movement attempts, the data from channels 6, 8, 10, 11 and 13 were re-referenced to channel 9, then, passed...
through a 50 Hz notch-filter and a 4-200 Hz second-order Butterworth bandpass filter. Then, the decibel normalized spectral power of 5 Hz bins between 12-70 Hz were calculated using the Thompson multi-taper method. These features were averaged, then passed through a 500 ms boxcar filter resulting in 1 feature per current data bin.

Classification layer
For participant 1, ten manually selected right quadriceps motor mapping task runs between day 68 and 85 post surgery were used to train a binary support vector machine (SVM). Separate datasets were used to train (24 trials), tune hyperparameters (18 trials) and test (16 trials) the SVM. The SVM was trained with gaussian radial basis functions. The optimal hyperparameters C and gamma (γ) were chosen such that they maximise the F1-score on the validation set. The test set was withheld from training and tuning the SVM and used only to evaluate the accuracy of the trained SVM. The SVM layer z-normalized the data per channel, per frequency bin, using the constants calculated from the training data, then, predicted the state of given data bin as either rest or movement-attempt.

For participant 2, a threshold classifier was used, where the classifier predicted a movement-attempt state if the feature signal reached a given threshold value. Low and high threshold levels were manually tuned, where the former was closer to the baseline than the latter. If the system detected that the participant was typing by monitoring keystrokes, the threshold level was automatically set to the lower level. The threshold level defaulted back to high if typing was not detected for 15 s and at all other times. This design was intended to ease the criteria for typing where more consecutive click events were expected compared to general computer control.

Click-logic layer
For both participants, the predictions from the classification layer were passed through the click-logic layer which translated the sequences of classification predictions into three command outputs; no click, short click, and long click. Short clicks were generated when 3-9 consecutive movement-attempt predictions were immediately followed by a rest prediction. Long clicks were initiated on the 10th consecutive movement attempt predictions and the command was released on the subsequent rest prediction. This design allowed the participants to “click-hold-and-release” and control the screen magnification function for making fine-scale selections. All other events resulted in no clicks.

Multiclass classification
Offline analysis revealed above chance-level multiclass classification. For participant 1, signals recorded on channels 4, 10 and 13 from the right hand and right quadriceps motor mapping data were re-referenced to channel 16. Normalised spectral power of 2 Hz bins between 4-30 Hz, 60-80 Hz and 120-180 Hz were
extracted as features to classify rest, right quadriceps and right hand movement attempts. Rest period was defined as -4 s and -1 s from the attempt cue onset, and movement attempt period was between 1 s-4 s. Data window size was 500 ms with a 100 ms stride, resulting in 30 rest samples and 30 movement attempt samples per trial, per movement type. SVM training/tuning and testing set were randomly permuted 50 times without sequence repeats for cross validation of decoder performance. There were 19200 training and 4800 testing samples from mutually exclusive set of recordings per iteration. Across 50 iterations, the median precision, recall and F1-score were 0.30 (0.29-0.31), 0.66 (0.64-0.68) and 0.41 (0.40-0.43) for rest; 0.78 (0.77-0.80), 0.54 (0.53-0.54) and 0.64 (0.62-0.65) for right quadriceps; 0.87 (0.84-0.88), 0.53 (0.52-0.54) and 0.65 (0.64-0.66) for right hand; and 0.65 (0.64-0.66), 0.58 (0.56-0.59) and 0.57 (0.56-0.58) overall. All median values, except for rest precision, were higher than the 3-class chance-level of 0.35 derived using a binomial cumulative distribution with sample size of 4800 (\(\alpha = 0.001\); Fig. S5A). The process was repeated for participant 2, except signals recorded on channels 4, 6, 8, 10, 13 and 14 from the left foot and right hand motor mapping data were re-referenced to channel 9 to classify between rest, left foot and right hand movement attempts. There were 8640 training and 2160 testing samples per iteration. Across 50 iterations, the median precision, recall and F1-score were 0.80 (0.78-0.81), 0.73 (0.71-0.75) and 0.76 (0.75-0.77) for rest; 0.61 (0.59-0.64), 0.66 (0.64-0.68) and 0.64 (0.62-0.65) for left foot; 0.42 (0.38-0.46), 0.48 (0.45-0.50) and 0.45 (0.42-0.48) for right hand; and 0.61 (0.59-0.63), 0.62 (0.61-0.64) and 0.62 (0.59-0.63) overall. All median values were higher than the 3-class chance-level of 0.36 derived using a binomial cumulative distribution with sample size of 1920 (\(\alpha = 0.001\); Fig. S5B).

**TASKS AND DIGITAL DEVICE CONTROL**

The participants achieved task and real-world device control by controlling the cursor using an eye-tracker and no, short, and long click actions using the motor prosthesis through alternate access programs (Communicator-5, and Windows Control, Tobii Dynavox). For participant 2, the direct visual feedback was turned off when practicing system control. For the typing task, keys on a virtual keyboard could be pressed by moving the cursor to the target and clicking on the keys using either the short or long click actions. For the email, texting, shopping and finance task and for home-use, a mouse action type could be chosen from a selection bar and the action could be performed by moving the cursor to the target using the eye-tracker and controlling them with the short click or the long click. The long click allowed the participant to zoom into the screen and perform the chosen mouse action on the target item, in turn, allowing the participant to interact with small items on the screen without having to change the screen resolution or use limited field-of-view applications.
Performance testing

The accuracy of the selections made, click selection accuracy, was defined as:

\[
\text{click selection accuracy} = \frac{S_{\text{total}} - S_{\text{error}}}{S_{\text{total}}}
\]

where \(S_{\text{total}}\) is total number of selections and \(S_{\text{error}}\) is the total number of errors. Typographical, spelling, and eye-tracker related errors that may have been intentionally selected were counted as errors.

The rate of erroneous selections made, click selection errors, was defined as:

\[
\text{click selection errors} = 1 - \text{click selection accuracy}
\]

Click selection accuracy and click selection errors are presented as percentages in results.

The rate of correct characters per minute or CCPM, was defined as:

\[
\text{CCPM} = \frac{S_{\text{total}} - S_{\text{error}}}{t}
\]

where \(t\) is the sum of the elapsed time to make all the selections in minutes.

Bits/trial, \(B\), was defined as per[4]:

\[
B = \log_2 N + P \log_2 P + (1 - P) \log_2 \left( \frac{1 - P}{N - 1} \right)
\]

where \(N\) is the total number of symbols to select from, \(P\) is the probability that the symbols are correctly chosen and is equal to click selection accuracy per trial. Equal error probability is assumed for each symbol (i.e., \(\frac{1-P}{N-1}\)).

The information transfer rate, ITR, was calculated as:

\[
\text{ITR} = \frac{B}{t_{\text{trial}}}
\]

where \(t_{\text{trial}}\) is the average time taken to make a single selection in seconds. \(B\) and ITR were calculated for the motor neuroprosthesis + eye-tracker, by setting \(N\) as the total number of keys on the virtual keyboard used (\(N = 31\)). The isolated contribution of the motor neuroprosthesis to \(B\) and ITR was estimated by setting \(N\) as the total number of commands actionable using the decoder (\(N = 3\)) as the number of available commands persists across keys.

Instrumental Activities of Daily Living (IADL) tasks

The texting task involved opening the WhatsApp from the desktop, clicking on the ‘contact search’ button, typing the recipient’s name, clicking on the recipient’s contact profile, typing “hello” and clicking the ‘send’ button. The email task involved opening Google Chrome from the desktop, clicking on the shortcut icon to Gmail, the ‘compose’ button, and the address bar, typing in the recipient’s email, clicking on the subject bar, typing “letter” and the email body, typing “G’day from <location>!” (<location> was replaced with the participant’s home town), clicking on the emoji button, the smiley-face emoji icon, and the attachment button, searching and attaching for a pre-defined file in the attachment prompt window, clicking the “Send” button on the email webpage, and then closing the browser.

The shopping task involved opening Google Chrome, navigating to
amazon.com.au, searching for “jumper”, clicking on a desired item, picking a size, adding the item to the cart, searching for “ramp”, clicking on a desired item, adding the item to the cart, then clicking on ‘check out’. No items were purchased. The finance task involved opening Google Chrome, navigating to their internet banking website, logging on and checking the balance. Given the qualitative nature of these tasks, the performance was measured as either successful or unsuccessful.
# SUPPLEMENTARY TABLES AND FIGURES

## Table 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis of spinal cord injury (SCI), amyotrophic lateral sclerosis (ALS), stroke or muscular dystrophy.</td>
<td>Has dementia or cognitive impairment sufficient to impair capacity to provide informed consent or which could impact ability to comply with investigational requirements (eg: MMSE &lt;24, ECAS or other determination made by Investigator)</td>
</tr>
<tr>
<td>Diagnosed for at least six (6) months and if SCI, at least twelve (12) months</td>
<td>For ALS participants, has NOT had a formal capacity assessment by a professional with experience in capacity assessment (psychiatrist, neurologist, psychologist) within 90 days of Screen1 visit, which assesses capacity to consent and excludes Frontotemporal dementia</td>
</tr>
<tr>
<td>Life expectancy of at least twelve (12) months in the opinion of the treating physician</td>
<td>Chronic oral or intravenous steroids or immunosuppressive therapy or other therapy/clinical condition that severely reduces immunity</td>
</tr>
<tr>
<td>Pattern of complete or incomplete quadriplegic weakness with associated functional impairment, with specific cord level MRC weakness of at least:</td>
<td>Based on the enrolling physician’s opinion, has unrealistic expectations regarding the possible benefits, risks and limitations associated with the implantation or surgical procedures</td>
</tr>
<tr>
<td>• C5 &lt;= 4/5 grade</td>
<td></td>
</tr>
<tr>
<td>• C6 &lt;= 2/5 grade</td>
<td></td>
</tr>
<tr>
<td>• C7-T1 &lt;= 1/5 grade</td>
<td></td>
</tr>
<tr>
<td>If the participant has a diagnosis of ALS the participant may have 4/5 grade weakness with functional impairment and must report subjective decline over preceding four months</td>
<td></td>
</tr>
<tr>
<td>Participants with ALS must have:</td>
<td></td>
</tr>
<tr>
<td>• Confirmed clinical diagnosis of “Clinically Definite ALS”, “Clinically Probable ALS”, “Clinically Probable-Laboratory Supported ALS” not caused by HIV.</td>
<td>Has been hospitalized for a psychiatric condition with the preceding two (2) years or has had a history of psychosis within the preceding two (2) years</td>
</tr>
<tr>
<td>• Advanced Care Directive in place before insertion of device.</td>
<td></td>
</tr>
<tr>
<td>• Assessment by specialist supporting service regarding respiratory function and potential use of non-invasive ventilation</td>
<td></td>
</tr>
<tr>
<td>No conditions, including an eye movement disorder, that would prevent the use of eye tracking software and has a level of vision that will not impede viewing of screens and visualisations</td>
<td>Is deemed unsuitable by a specialist anaesthesiologist or respiratory physician to undergo a general anaesthetic (ie FVC &lt; 60%)</td>
</tr>
<tr>
<td>Has normal venous sinus anatomy, with two patent jugular veins (of sufficient size for the device) and bilateral patent transverse sinuses as evidenced by MR venography (MRV) or CT venography (CTV) within the last six (6) months or if vascular anatomy is unknown, is willing to undergo an MRV or CTV assessment to assess vascular suitability for endovascular device placement</td>
<td>Has findings on MRV deemed incompatible, by an experienced neurointerventionalist, with device implantation in the SSS (eg: isolated dominant, superior anastomotic vein (vein of Trolard))</td>
</tr>
<tr>
<td>Evidence of activation, under fMRI testing, of motor cortical areas adjacent to the superior sagittal sinus</td>
<td>Has a contraindication to angiographic imaging, including chronic kidney injury (CKI - eGFR &lt; 60mls/min)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has a history of Deep Vein Thrombosis (DVT) or on hormone therapy (eg: HRT)</td>
<td></td>
</tr>
<tr>
<td>Has any bleeding disorders (tests required if clinical status unknown) or is resistant to aspirin and/or clopidogrel or has any contraindication that precludes antithrombotic treatment</td>
<td></td>
</tr>
<tr>
<td>Has an active implanted stimulation device (eg: pacemaker, deep brain stimulator, spinal cord stimulator)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Trial average system control performance

<table>
<thead>
<tr>
<th>Par. 1</th>
<th>Trials (Words)</th>
<th>Selections</th>
<th>Errors</th>
<th>Duration (s)</th>
<th>Duration/Selection (s)</th>
<th>Click selection accuracy (%)</th>
<th>Click selection error (%)</th>
<th>CCPM</th>
<th>MN Bit/trial</th>
<th>MN ITR bits s⁻¹</th>
<th>MN + ET ITR bits s⁻¹</th>
<th>Text Task</th>
<th>Email Task</th>
<th>Shopping Task</th>
<th>Finance Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum</td>
<td>129</td>
<td>748</td>
<td>68</td>
<td>3211.23</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24.89</td>
<td>4.34</td>
<td>92.63</td>
<td>7.37</td>
<td>13.81</td>
<td>1.31</td>
<td>0.32</td>
<td>4.39</td>
<td>1.08</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9.71</td>
<td>1.33</td>
<td>15.22</td>
<td>15.22</td>
<td>4.33</td>
<td>0.43</td>
<td>0.13</td>
<td>0.96</td>
<td>0.36</td>
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</tr>
<tr>
<td>Min</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9.91</td>
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<td>0.05</td>
<td>0.01</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Q1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>17.96</td>
<td>3.35</td>
<td>87.50</td>
<td>0.00</td>
<td>10.96</td>
<td>0.92</td>
<td>0.24</td>
<td>3.80</td>
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SD = standard deviation; CCPM = correct characters per minute; ITR information transfer rate; MN = motor neuroprosthesis; ET = Eye tracker
Figure S1. Implantable components
Panel A shows the stent-head (S). Panel B shows the Stentrode stent-head (S), transmission lead (L), and proximal connector (P). Panel C shows the internal telemetry unit (ITU) showing the location of the Stentrode insertion (arrow) and the hermetically encapsulated telemetry chip (T).
**Figure S2. Endothelialisation of Stentrode implanted in chronic animal trial**

Histopathological hematoxylin and eosin stained sections of a sheep vessel implanted with a Stentrode implanted for durations of A) 3 days and B) 45 days showing vessel patency and incorporation of stent struts by 45 days. C) Histopathologically assessed endothelium as a function of implant time for stent segments assessed at the proximal (Prox., white), middle (Mid., grey) and distal (Dist., dark grey) stent locations for animals implanted for 3 days (n=2, clear bars) and 45 days (n=4, dashed bars). C) The percentage of intact endothelium was 0% across all positions for both animals assessed 3 days post implant, increasing to 90.0±10.0%, 88.8±11.3%, and 97.5±1.4% (mean±SEM) for the proximal, middle and distal sections, respectively for animals implanted for 45 days. D) The percentage of intima lined by an acute fibrin layer was 57.5±22.5%, 37.5±12.5%, and 40.0±15.0 (mean±SEM, n=2) for the proximal, middle and distal sections, respectively, in animals implanted for 3 days. Stent struts were covered (100%) in neointima in all animals implanted for 45 days across all positions.
**Figure S3. Custom decoder**

The decoder takes a window of data every 100 ms from selected feature channels, then passes it through the preprocessing, classification, and click-logic layer. The preprocessing layer extracts normalised spectral power as features. The classification layer then predicts the current set of features as either rest or movement-attempt. Finally, the click-logic layer outputs no clicks, short clicks, or long clicks, based on the sequence of classification outputs. If between 3 and 9 consecutive movement-attempts are immediately followed by a rest classification, short clicks are generated. Long clicks are initiated upon the 10th consecutive movement attempt classifications and are released upon a subsequent rest classification. All other sequences of events result in no clicks.
**Figure S4. Motor mapping of movement-attempts**

Panel A shows a box plot of offline decoding accuracy of various movement-attempts performed by participant 1 during motor mapping task in sessions 1-12, averaged across 50 random permutations. Unique combinations of runs were chosen for SVM training and tuning at each random permutation. The test set runs were fixed after initial randomisation with at least 810 samples. Orange lines depict medians and the box outlines the 1\textsuperscript{st} and 3\textsuperscript{rd} quartile, whiskers depict range, and circles depict outliers. Panel B shows the trial mean spectrogram during motor mapping task as t-scores for ease of cross-frequency visualisation, averaged across feature channels 4, 10 and 13. Green line depicts the transition point from attempt to rest blocks.
Figure S5. Classification of various movement-attempt types

Panel A shows the box plots of offline multiclass decoding performance metrics across 50 random permutations for patient 1 and Panel B for patient 2. Unique combinations of runs were chosen for SVM training/tuning and testing at each random permutation. The orange line depicts the median and the box outlines the 1st and 3rd quartiles, and whiskers depict the range. The blue dashed line shows the 3-class chance-level derived using a binomial cumulative distribution at alpha=0.001. n above box plots denotes number of samples. The spectrograms show the z-normalised spectral power evolution centred around the movement-attempt cue onset. n above spectrograms denotes the number of epochs.
SUPPLEMENTARY VIDEOS

Video S1. Neurointerventional procedure and device implant vignette
https://synchron.egnyte.com/dl/5WM6lOmgug

Video S2. Motor neuroprosthesis performance and utilisation vignettes
https://synchron.egnyte.com/dl/NhihAUzACw

- Vignette 1 - Remote texting caregiver: 0 mins
- Vignette 2 - Playing music: 1 mins 40 secs
- Vignette 3 - Internet browsing: 2 mins 28 secs
- Vignette 4 - Typing task: participant 1: 3 mins 10 secs
- Vignette 5 - Typing task: participant 2: 5 mins 05 secs
- Vignette 5 - Text task: 6 mins 10 secs
- Vignette 6 - Email task: 7 mins 20 secs
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PRECLINICAL DATA

Endothelialization
An animal study was performed to demonstrate rates of endothelialization using an identical test article to that implanted in the human participant. Experiments were performed in accordance with FDA Regulations of Good Laboratory Practices for Nonclinical Laboratory Studies CFR Title 21 Part 58 and applicable NIH and NCI Standard Operating Procedures. Sheep (Merino ewes), were implanted with a Stentrode within a clinically-relevant sized vessel (6 mm jugular vein). The Stentrode was delivered using the coaxial catheter system designed for human use, and animals were terminated at day 3 (n=2) and day 45 (n=4), perfused, stained with Haematoxylin and Eosin and embedded in plastic or paraffin (APS, MN). 3-day subjects presented with completely denuded endothelium and thin segmental fibrin deposition. Although endothelial tissue loss presented, there was no exhibited injury to the vascular walls, deemed typical of an acute time point by the contracted agency. 45-day subjects demonstrated maturation of neointimal tissue that was expected of an extended time point. Microscopic fibrin deposition was observed on the intima and struts of the recording head, with 95% of device covered by 45 days (Fig. S1).
PARTICIPANT

Ethics and regulatory approval
This was a first-in-human, single arm, open-label, prospective study approved by the Human Research Ethics Committee of St Vincent’s Hospital, Victoria, Australia, in November 2018. Subsequent Research Governance Office approval was granted by The Royal Melbourne Hospital in January 2019. The Research Governance Office approval for the clinical recruiting site, Calvary Health Care Bethlehem, was granted in December 2018. Approval was granted under the Clinical Trial Notification (CTN) scheme of the Therapeutic Goods Administration (TGA) Australia (CTN Repository CT-2018-CTN-02369-1 v1.0) on 29th November 2018.

Recruitment
As per the inclusion criteria, participants with a motor score of >4/5 must report a subjective decline of upper limb extremity in the preceding four months resulting in functional impairment. The participants underwent screening to confirm eligibility and consented to the study. Inclusion criteria were satisfactorily met, including assessment of an fMRI demonstrating activation of primary motor cortex immediately adjacent to the superior sagittal sinus as well as an MR head and neck venography that demonstrated bilateral patent transverse sinuses and jugular veins by an interventional neuroradiologist (PM) and vascular neurologist (BC). Participants were assessed by a neurologist specialising in frontotemporal dementia (SL) to exclude dementia and assess capacity for informed consent. A respiratory assessment including pulmonary function tests and sleep study was performed. If follow up appointments satisfied anesthesia screening criteria the participants would progress to a final confirmation of suitability for general anesthetic and suitability for the procedure 2 weeks before implant. All other inclusion criteria were confirmed on day -1, with no exclusion criteria being met and the participant underwent the implantation via angiography. The participants were commenced on aspirin 300 mg daily and 75 mg of clopidogrel 14 days prior to the procedure. For participant 1, a point-of-care antiplatelet resistance test was performed seven days prior (VerifyNow, Accumetrics, CA), which revealed 11% resistance to clopidogrel. The decision was made by the treating interventional neuroradiologist (PM) to increase the dose to 150 mg daily. Repeat testing immediately prior to the procedure revealed adequate platelet inhibition of 30%.

Patient reported outcomes
Participant 1
At baseline, quality of life score (EQ-5D-5L) of 73 out of 100, reduced to 72/100 at day-7 post implant, and 70/100 at day-14 post-implant. This was maintained to month-4 follow-up and reduced at month-5 and month-6 follow-up at 65, further
reducing to 50/100 at month-12 follow-up. Hospital Anxiety and Depression Scale (HADS) score at baseline was D=3 and A=5. Over the duration of the trial a normal HADS score was maintained, although elevated compared to baseline (A=6/D=7) at month-12. Visual Analogue Scale (VAS) score, at baseline 0 out of 10, elevated post procedure to 1/10 from day-7 to day-21 post implant, returning to baseline from day-28 to month-5. VAS score increased at month-6 to 2/10 and 3/10 at month-12, with the patient reporting muscle pain secondary to progression of motor neuron disease.

Participant 2
The baseline quality of life score (EQ-5D-5L) was 45/100, increasing to 70/100 post-implant at day-14 follow up, reducing at day-28 to 65/100, increasing for month-2 and month-3 to 70/100 and reducing to 65 at month-4 follow up visit. Visual analogue numeric pain distress scale (VAS) at baseline scored 0/10. During follow-up the VAS was elevated at day-28 to 2/10 and returned to baseline for month-2 and month-4. HADS score measured at baseline of D=2 and A=5 and maintained normal levels throughout to month-4 follow up (A=3 D=2).

**IMAGING-GUIDED DEVICE DELIVERY**

**Pre-operative MRI acquisition (MRI venography and functional MRI)**
A pre-operative MRI investigation of the cortical and vascular structures, and cortical motor function was performed inside a Siemens MAGNETOM Prisma 3T scanner. The participant’s vital signs were monitored, and communication was achieved through a two-way intercom while he was inside the scanner. The structural volumes were acquired using a contrast-enhanced (C+MPRAGE) and non-contrast enhanced magnetization prepared rapid gradient echo (MPRAGE) sequence, and contrast-enhanced Time-resolved angiography With Interleaved Stochastic Trajectories (TWIST) sequence. The acquired volumes were utilized to inform decisions regarding participation eligibility and implantation planning. Two sets of functional volumes were acquired using a gradient-echo echo-planar imaging (GE-EPI) sequence while the participant performed a lower-limb motor task. The participant was presented with instructions on the screen to either “rest” or “attempt”. The task in the first and second set was to tap their right foot (repeated ankle plantar flexion and relaxation) and left foot, respectively, at a rate of ~1 Hz. Both rest and attempt blocks lasted for 15 s each. There were eight attempt and nine rest blocks as each experiment began and finished with a rest trial. The participant practiced the task outside of the scanner and were given verbal instructions prior to the scan via the intercom.

**Co-registration of deployment target markers for implantation**
Regions of significant Blood-Oxygenation-Level-Dependent (BOLD) signal fluctuation during the left and right lower limb movements were identified by fitting
a General Linear Model (GLM) to each dataset. Z-score maps were generated by contrasting the attempt and rest blocks for each functional set. The resulting BOLD activation maps for left and right foot tapping were co-registered to the C+MPRAGE space. The dorsomedial Primary Motor Cortex (M1) was identified in the C+MPRAGE volume based on the structural information and guided by the functional information by a neuroradiologist (PM). Three guide markers for device deployment were identified in the C+MPRAGE space. The portion of the superior sagittal sinus (SSS) immediately superior to the posterior margin of the dorsomedial M1 was marked (i.e., M1 marker). The anterior and posterior markers were placed 18 mm anterior and 22 mm posterior to the M1 marker, respectively (A and P marker; the total length of the recording head is 40mm). These markers encompassed portion of the Supplementary Motor Cortex (SMA), the M1 and the Primary Somatosensory cortex (S1), denoting the ideal deployment region of the stent electrode array for recording motor-related signals[1,2]. The C+MPRAGE volume with the three device deployment targets was co-registered to the pre-contrast 3D-Digital Subtraction Angiography (3D-DSA) volume acquired intraoperatively. Siemens’ automatic co-registration algorithm was used, and the result was visually inspected by the interventionalist.

**Endovascular device deployment**

The participant was admitted to the Royal Melbourne Hospital the evening prior to the procedure and CT head and neck with contrast was performed as a baseline non-invasive venography study. The participant was placed under general anaesthesia and the angiography procedure was commenced. The co-registration of fMRI of data points on a structural MRI were used to generate an anatomical target using the roadmap function utilising the contrast-enhanced rotational 3D-DSA. A working view on the lateral plane on one image intensifier was set and utilised to overlay the roadmap with the anatomical targets (A, P and M1). The internal jugular vein was visualised under ultrasound guidance and punctured immediately above the clavicle, in between the two heads of the sternocleidomastoid muscle. A 6-French sheath (Pinnacle, Terumo) was exchanged over a microwire into the jugular vein. 5000 units of intravenous heparin were administered. Under DSA visualisation a coaxial catheter system (Fathom 16 microwire, Boston Scientific, MN; 3Max, 6-French Benchmark, Penumbra, CA) was advanced to the target location in the superior sagittal sinus. Venous tortuosity due to arachnoid granulations had been anticipated following their visualisation on the baseline CT venography. This resulted in minor resistance to the advancing 6-French catheter. Once the catheter was in position, the stent electrode array (Stentrode, Synchron, CA) was preloaded into a custom designed 4-French delivery sheath with radio-opaque tip (Synchron, CA), flushed with normal saline and advanced inside the guiding catheter. The delivery sheath was advanced to a position 10 mm beyond anatomical target A. The 6-French guide catheter was
retracted to the proximal superior sagittal sinus, leaving the delivery sheath in position. The delivery sheath was then retracted and positioned to match anatomical target A with the distal marker. The stent electrode array was then unsheathed, utilising the high radio-opacity of the cable to ensure correct positioning during deployment in the superior sagittal sinus with symmetric wall apposition (Fig. 2; Video S1). Repeat angiography demonstrated unimpaired blood flow through the Stentrode, with visualisation of an arachnoid granulation penetrating through a cell in the stent-head, resulting in anchoring of the device in position. The coaxial catheter system was removed, and gentle manual compression was held over the jugular vein to achieve haemostasis around the transvascular lead. The extension lead was unscrewed from the proximal portion, and the transmission lead exiting the vessel was tunnelled subcutaneously into a chest pocket. The proximal end was connected to the ITU (Synchron, CA) and the unit was implanted into the subcutaneous chest pocket immediately inferior to the left clavicle. Under sterile conditions in the angiography suite, the ETU was transiently placed above the ITU and the system check confirmed data was flowing. The participant was extubated in the angiography suite, monitored in the Intensive Care Unit and discharged home two days later.

**DECODER**

**Parameter optimisation**

**Participant 1**

Motor mapping task runs with a variety of movements were performed over the 12 sessions between day 50 and day 86 post-surgery. The data was used to determine the ideal strategy for BCI control and optimise the parameters of the preprocessing and classification layer based on decoding accuracy. Offline binary classification accuracy of left foot, right foot and right quadriceps movement attempt was assessed through random permutation. Across 50 iterations, a binary SVM was trained using a unique combination of training and validation dataset and its accuracy was tested on a fixed test set for each movement type separately (the test sets were initially randomly sampled and remained fixed through the iterations, and there were at least 810 samples to classify). The results revealed that the right quadriceps movement attempts yielded the highest accuracy averaged across the permutations (78.7±1.2%; mean±SD), compared to right (66.5±5.7%, Wilcoxon rank-sum test $p=6.9006\times10^{-18}$) and left foot tapping attempts (55.5±2.3%, $p=6.6045\times10^{-18}$; **Fig. S5**). Thus, we focused on the right quadricep movement attempts for future sessions. Between sessions 12 and 13, several typing tasks were performed using this decoder to optimise the parameters of the click-logic layer in the decoder. The decoder parameters were fixed from session 13 (day 92 post-surgery). All hyperparameters, except for C and $\gamma$ of the SVC were manually optimised.
Participant 2
Based on acquired knowledge from participant 1, it was deemed that direct visual feedback of features may help with training. However, high dimensional features that worked well for the SVM could not be visualised. Considering these factors, along with the success of extending binary classification events into two discrete outputs based on duration of control (i.e., click-logic layer), we employed a threshold decoder that took a 1D average spectral feature as an input that could be directly visualised. The ideal control strategy, feature channels and frequency bands described above were chosen based on the highest correlation values between the motor mapping tasks and spectral power of specific bipolar pair channels calculated from specific movement attempt types in session 1. The participant practiced controlling the 1D average spectral feature across the threshold levels with direct visual feedback, and the normalization constants and threshold values were fine-tuned session to session. The participant could also manually calibrate the normalization constants himself by clicking on the F11 key when using the system, which took 30 s.

General design
Raw data was sampled at 2 kHz per channel and was passed through the decoder comprised of three layers, preprocessing layer, classification layer, and click-logic layer (Fig. S2). The preprocessing layer removed large artifacts and disconnection events using thresholds in temporal and spectral domain and extracts spectral power as features. The classification layer predicted whether the features represented the state of rest or movement-attempts. The click-logic layer translated sequences of prediction events from the classifier into three outputs, no click, short click and long click. Hyperparameters of the decoders were manually tuned through trial and error and exploring the motor mapping task data. Participant specific settings for the decoder used for testing are provided below.

Preprocessing layer
For participant 1, the spectral features were extracted from a 100 ms window at 100 ms strides (i.e., every 100 ms). To capture neural correlates of right quadriceps movement attempts, the data from channels 4, 10 and 13 were re-referenced to channel 16 then passed through a 50 Hz notch-filter for line-noise removal and a 4-30 Hz second second-order Butterworth bandpass filter. Then, the decibel normalized spectral power of 1 Hz bins between 4-30 Hz were calculated using the Thompson multi-taper method. Finally, the data bins were passed through a 1 s boxcar filter (across time), resulting in 78 features (3 channels x 26 frequency bins) per current data bin.

For participant 2, the spectral features were calculated from a 1000 ms window at 100 ms strides. To capture neural correlates of left foot movement attempts, the data from channels 6, 8, 10, 11 and 13 were re-referenced to channel 9, then, passed...
through a 50 Hz notch-filter and a 4-200 Hz second-order Butterworth bandpass filter. Then, the decibel normalized spectral power of 5 Hz bins between 12-70 Hz were calculated using the Thompson multi-taper method. These features were averaged, then passed through a 500 ms boxcar filter resulting in 1 feature per current data bin.

**Classification layer**

For participant 1, ten manually selected right quadriceps motor mapping task runs between day 68 and 85 post surgery were used to train a binary support vector machine (SVM). Separate datasets were used to train (24 trials), tune hyperparameters (18 trials) and test (16 trials) the SVM. The SVM was trained with gaussian radial basis functions. The optimal hyperparameters C and gamma (γ) were chosen such that they maximise the F1-score on the validation set. The test set was withheld from training and tuning the SVM and used only to evaluate the accuracy of the trained SVM. The SVM layer z-normalized the data per channel, per frequency bin, using the constants calculated from the training data, then, predicted the state of given data bin as either rest or movement-attempt.

For participant 2, a threshold classifier was used, where the classifier predicted a movement-attempt state if the feature signal reached a given threshold value. Low and high threshold levels were manually tuned, where the former was closer to the baseline than the latter. If the system detected that the participant was typing by monitoring keystrokes, the threshold level was automatically set to the lower level. The threshold level defaulted back to high if typing was not detected for 15 s and at all other times. This design was intended to ease the criteria for typing where more consecutive click events were expected compared to general computer control.

**Click-logic layer**

For both participants, the predictions from the classification layer were passed through the click-logic layer which translated the sequences of classification predictions into three command outputs; no click, short click, and long click. Short clicks were generated when 3-9 consecutive movement-attempt predictions were immediately followed by a rest prediction. Long clicks were initiated on the 10th consecutive movement attempt predictions and the command was released on the subsequent rest prediction. This design allowed the participants to “click-hold-and-release” and control the screen magnification function for making fine-scale selections. All other events resulted in no clicks.

**Multiclass classification**

Offline analysis revealed above chance-level multiclass classification. For participant 1, signals recorded on channels 4, 10 and 13 from the right hand and right quadriceps motor mapping data were re-referenced to channel 16. Normalised spectral power of 2 Hz bins between 4-30 Hz, 60-80 Hz and 120-180 Hz were
extracted as features to classify rest, right quadriceps and right hand movement attempts. Rest period was defined as -4 s and -1 s from the attempt cue onset, and movement attempt period was between 1 s-4 s. Data window size was 500 ms with a 100 ms stride, resulting in 30 rest samples and 30 movement attempt samples per trial, per movement type. SVM training/tuning and testing set were randomly permuted 50 times without sequence repeats for cross validation of decoder performance. There were 19200 training and 4800 testing samples from mutually exclusive set of recordings per iteration. Across 50 iterations, the median precision, recall and F1-score were 0.30 (0.29-0.31), 0.66 (0.64-0.68) and 0.41 (0.40-0.43) for rest; 0.78 (0.77-0.80), 0.54 (0.53-0.54) and 0.64 (0.62-0.65) for right quadriceps; 0.87 (0.84-0.88), 0.53 (0.52-0.54) and 0.65 (0.64-0.66) for right hand; and 0.65 (0.64-0.66), 0.58 (0.56-0.59) and 0.57 (0.56-0.58) overall. All median values, except for rest precision, were higher than the 3-class chance-level of 0.35 derived using a binomial cumulative distribution with sample size of 4800 (α = 0.001; Fig. S5A). The process was repeated for participant 2, except signals recorded on channels 4, 6, 8, 10, 13 and 14 from the left foot and right hand motor mapping data were re-referenced to channel 9 to classify between rest, left foot and right hand movement attempts. There were 8640 training and 2160 testing samples per iteration. Across 50 iterations, the median precision, recall and F1-score were 0.80 (0.78-0.81), 0.73 (0.71-0.75) and 0.76 (0.75-0.77) for rest; 0.61 (0.59-0.64), 0.66 (0.64-0.68) and 0.64 (0.62-0.65) for left foot; 0.42 (0.38-0.46), 0.48 (0.45-0.50) and 0.45 (0.42-0.48) for right hand; and 0.61 (0.59-0.63), 0.62 (0.61-0.64) and 0.62 (0.59-0.63) overall. All median values were higher than the 3-class chance-level of 0.36 derived using a binomial cumulative distribution with sample size of 1920 (α = 0.001; Fig. S5B).

**TASKS AND DIGITAL DEVICE CONTROL**

The participants achieved task and real-world device control by controlling the cursor using an eye-tracker and no, short, and long click actions using the motor prosthesis through alternate access programs (Communicator-5, and Windows Control, Tobii Dynavox). For participant 2, the direct visual feedback was turned off when practicing system control. For the typing task, keys on a virtual keyboard could be pressed by moving the cursor to the target and clicking on the keys using either the short or long click actions. For the email, texting, shopping and finance task and for home-use, a mouse action type could be chosen from a selection bar and the action could be performed by moving the cursor to the target using the eye-tracker and controlling them with the short click or the long click. The long click allowed the participant to zoom into the screen and perform the chosen mouse action on the target item, in turn, allowing the participant to interact with small items on the screen without having to change the screen resolution or use limited field-of-view applications.
Performance testing

The accuracy of the selections made, *click selection accuracy*, was defined as:

\[
\text{click selection accuracy} = \frac{S_{\text{total}} - S_{\text{error}}}{S_{\text{total}}}
\]

where \(S_{\text{total}}\) is total number of selections and \(S_{\text{error}}\) is the total number of errors. Typographical, spelling, and eye-tracker related errors that may have been intentionally selected were counted as errors.

The rate of erroneous selections made, *click selection errors*, was defined as:

\[
\text{click selection errors} = 1 - \text{click selection accuracy}
\]

*Click selection accuracy and click selection errors* are presented as percentages in results.

The rate of correct characters per minute or *CCPM*, was defined as:

\[
\text{CCPM} = \frac{S_{\text{total}} - S_{\text{error}}}{t}
\]

where \(t\) is the sum of the elapsed time to make all the selections in minutes.

Bits/trial, \(B\), was defined as per[4]:

\[
B = \log_2 N + P \log_2 P + (1 - P) \log_2 \left( \frac{1 - P}{N - 1} \right)
\]

where \(N\) is the total number of symbols to select from, \(P\) is the probability that the symbols are correctly chosen and is equal to *click selection accuracy* per trial. Equal error probability is assumed for each symbol (i.e., \(\frac{1 - P}{N - 1}\)).

The information transfer rate, \(ITR\), was calculated as:

\[
ITR = \frac{B}{t_{\text{trial}}}
\]

where \(t_{\text{trial}}\) is the average time taken to make a single selection in seconds.

\(B\) and \(ITR\) were calculated for the motor neuroprosthesis + eye-tracker, by setting \(N\) as the total number of keys on the virtual keyboard used (\(N = 31\)). The isolated contribution of the motor neuroprosthesis to \(B\) and \(ITR\) was estimated by setting \(N\) as the total number of commands actionable using the decoder (\(N = 3\)) as the number of available commands persists across keys.

Instrumental Activities of Daily Living (IADL) tasks

The texting task involved opening the WhatsApp from the desktop, clicking on the ‘contact search’ button, typing the recipient’s name, clicking on the recipient’s contact profile, typing “hello” and clicking the ‘send’ button. The email task involved opening Google Chrome from the desktop, clicking on the shortcut icon to Gmail, the ‘compose’ button, and the address bar, typing in the recipient’s email, clicking on the subject bar, typing “letter” and the email body, typing “G’day from <location>!” (<location> was replaced with the participant’s home town), clicking on the emoji button, the smiley-face emoji icon, and the attachment button, searching and attaching for a pre-defined file in the attachment prompt window, clicking the “Send” button on the email webpage, and then closing the browser.

The shopping task involved opening Google Chrome, navigating to...
amazon.com.au, searching for “jumper”, clicking on a desired item, picking a size, adding the item to the cart, searching for “ramp”, clicking on a desired item, adding the item to the cart, then clicking on ‘check out’. No items were purchased. The finance task involved opening Google Chrome, navigating to their internet banking website, logging on and checking the balance. Given the qualitative nature of these tasks, the performance was measured as either successful or unsuccessful.
### SUPPLEMENTARY TABLES AND FIGURES

#### Table 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>Clinical diagnosis of spinal cord injury (SCI), amyotrophic lateral sclerosis (ALS), stroke or muscular dystrophy.</td>
<td>Has dementia or cognitive impairment sufficient to impair capacity to provide informed consent or which could impact ability to comply with investigational requirements (eg: MMSE &lt;24, ECAS or other determination made by Investigator)</td>
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<tr>
<td>Diagnosed for at least six (6) months and if SCI, at least twelve (12) months</td>
<td>For ALS participants, has NOT had a formal capacity assessment by a professional with experience in capacity assessment (psychiatrist, neurologist, psychologist) within 90 days of Screen1 visit, which assesses capacity to consent and excludes Frontotemporal dementia</td>
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<tr>
<td>Life expectancy of at least twelve (12) months in the opinion of the treating physician</td>
<td>Chronic oral or intravenous steroids or immunosuppressive therapy or other therapy/clinical condition that severely reduces immunity</td>
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<tr>
<td>Pattern of complete or incomplete quadriplegic weakness with associated functional impairment, with specific cord level MRC weakness of at least:</td>
<td>Based on the enrolling physician’s opinion, has unrealistic expectations regarding the possible benefits, risks and limitations associated with the implantation or surgical procedures</td>
</tr>
<tr>
<td>• C5 &lt;= 4/5 grade</td>
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<tr>
<td>• C6 &lt;= 2/5 grade</td>
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<tr>
<td>• C7-T1 &lt;= 1/5 grade</td>
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<tr>
<td>If the participant has a diagnosis of ALS the participant may have 4/5 grade weakness with functional impairment and must report subjective decline over preceding four months</td>
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<td>Participants with ALS must have:</td>
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</tr>
<tr>
<td>• Confirmed clinical diagnosis of “Clinically Definite ALS”, “Clinically Probable ALS”, “Clinically Probable-Laboratory Supported ALS” not caused by HIV.</td>
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<tr>
<td>• Advanced Care Directive in place before insertion of device.</td>
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<td>• Assessment by specialist supporting service regarding respiratory function and potential use of non-invasive ventilation</td>
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<tr>
<td>No conditions, including an eye movement disorder, that would prevent the use of eye tracking software and has a level of vision that will not impede viewing of screens and visualisations</td>
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<td>Is deemed unsuitable by a specialist anaesthesiologist or respiratory physician to undergo a general anaesthetic (ie FVC &lt; 60%)</td>
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<tr>
<td>Has normal venous sinus anatomy, with two patent jugular veins (of sufficient size for the device) and bilateral patent transverse sinuses as evidenced by MR venography (MRV) or CT venography (CTV) within the last six (6) months or if vascular anatomy is unknown, is willing to undergo an MRV or CTV assessment to assess vascular suitability for endovascular device placement</td>
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<td>Has findings on MRV deemed incompatible, by an experienced neurointerventionalist, with device implantation in the SSS (eg: isolated dominant, superior anastomotic vein (vein of Trolard))</td>
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<tr>
<td>Evidence of activation, under fMRI testing, of motor cortical areas adjacent to the superior sagittal sinus</td>
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<tr>
<td>Has a contraindication to angiographic imaging, including chronic kidney injury (CKI - eGFR &lt; 60mls/min)</td>
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<tr>
<td><strong>Has a history of Deep Vein Thrombosis (DVT) or on hormone therapy (eg: HRT)</strong></td>
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<tr>
<td><strong>Has any bleeding disorders (tests required if clinical status unknown) or is resistant to aspirin and/or clopidogrel or has any contraindication that precludes antithrombotic treatment</strong></td>
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<td><strong>Has an active implanted stimulation device (eg: pacemaker, deep brain stimulator, spinal cord stimulator)</strong></td>
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Table 2. Trial average system control performance

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<th>Trials (Words)</th>
<th>Selections</th>
<th>Errors</th>
<th>Duration (s)</th>
<th>Duration/Selection (s)</th>
<th>Click selection accuracy (%)</th>
<th>Click selection error (%)</th>
<th>CPM</th>
<th>MN Bit/trial</th>
<th>MN ITR bits s⁻¹</th>
<th>MN + ET ITR bits s⁻¹</th>
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<th>Email Task</th>
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</table>

SD = standard deviation; CPM = correct characters per minute; ITR information transfer rate; MN = motor neuroprosthesis; ET = Eye tracker
Figure S1. Implantable components
Panel A shows the stent-head (S). Panel B shows the Stentrode stent-head (S), transmission lead (L), and proximal connector (P). Panel C shows the internal telemetry unit (ITU) showing the location of the Stentrode insertion (arrow) and the hermetically encapsulated telemetry chip (T).
Figure S2. Endothelialisation of Stentrode implanted in chronic animal trial

Histopathological hematoxylin and eosin stained sections of a sheep vessel implanted with a Stentrode implanted for durations of A) 3 days and B) 45 days showing vessel patency and incorporation of stent struts by 45 days. C) Histopathologically assessed endothelium as a function of implant time for stent segments assessed at the proximal (Prox., white), middle (Mid., grey) and distal (Dist., dark grey) stent locations for animals implanted for 3 days (n=2, clear bars) and 45 days (n=4, dashed bars). C) The percentage of intact endothelium was 0% across all positions for both animals assessed 3 days post implant, increasing to 90.0±10.0%, 88.8±11.3%, and 97.5±1.4% (mean±SEM) for the proximal, middle and distal sections, respectively for animals implanted for 45 days. D) The percentage of intima lined by an acute fibrin layer was 57.5±22.5%, 37.5±12.5%, and 40.0±15.0 (mean±SEM, n=2) for the proximal, middle and distal sections, respectively, in animals implanted for 3 days. Stent struts were covered (100%) in neointima in all animals implanted for 45 days across all positions.
Figure S3. Custom decoder

The decoder takes a window of data every 100 ms from selected feature channels, then passes it through the preprocessing, classification, and click-logic layer. The preprocessing layer extracts normalised spectral power as features. The classification layer then predicts the current set of features as either rest or movement-attempt. Finally, the click-logic layer outputs no clicks, short clicks, or long clicks, based on the sequence of classification outputs. If between 3 and 9 consecutive movement-attempts are immediately followed by a rest classification, short clicks are generated. Long clicks are initiated upon the 10th consecutive movement attempt classifications and are released upon a subsequent rest classification. All other sequences of events result in no clicks.
Figure S4. Motor mapping of movement-attempts

Panel A shows a box plot of offline decoding accuracy of various movement-attempts performed by participant 1 during motor mapping task in sessions 1-12, averaged across 50 random permutations. Unique combinations of runs were chosen for SVM training and tuning at each random permutation. The test set runs were fixed after initial randomisation with at least 810 samples. Orange lines depict medians and the box outlines the 1st and 3rd quartile, whiskers depict range, and circles depict outliers. Panel B shows the trial mean spectrogram during motor mapping task as t-scores for ease of cross-frequency visualisation, averaged across feature channels 4, 10 and 13. Green line depicts the transition point from attempt to rest blocks.
Figure S5. Classification of various movement-attempt types

Panel A shows the box plots of offline multiclass decoding performance metrics across 50 random permutations for patient 1 and Panel B for patient 2. Unique combinations of runs were chosen for SVM training/tuning and testing at each random permutation. The orange line depicts the median and the box outlines the 1st and 3rd quartiles, and whiskers depict the range. The blue dashed line shows the 3-class chance-level derived using a binomial cumulative distribution at alpha=0.001. n above box plots denotes number of samples. The spectrograms show the z-normalised spectral power evolution centred around the movement-attempt cue onset. n above spectrograms denotes the number of epochs.
SUPPLEMENTARY VIDEOS

Video S1. Neurointerventional procedure and device implant vignette
https://synchron.egnyte.com/dl/5WM6lOmgug

Video S2. Motor neuroprosthesis performance and utilisation vignettes
https://synchron.egnyte.com/dl/NhihAUzACw

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<tr>
<th>Vignette</th>
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<td>Remote texting caregiver</td>
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</tr>
<tr>
<td>Vignette 2</td>
<td>Playing music</td>
<td>1 mins 40 secs</td>
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<tr>
<td>Vignette 3</td>
<td>Internet browsing</td>
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<td>Text task</td>
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<td>Vignette 6</td>
<td>Email task</td>
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REFERENCES

1 Yoo PE, Oxley TJ, John SE, et al. Feasibility of identifying the ideal locations for motor intention decoding using unimodal and multimodal classification at 7T-fMRI. *Scientific Reports* 2018;8:15556. doi:10.1038/s41598-018-33839-4

